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GUEST EDITORIAL

Is Cryosurgery Appropriate Treatment for Hepatic Malignancies?

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Management of primary and metastatic cancers involving the liver has evolved greatly over the past few decades. The diagnosis of liver metastases or primary cancer of the liver was formerly a death sentence; with increasing knowledge of hepatic anatomy, however, resection of involved segments, lobes, and even more of the liver has become feasible. At times, even total hepatectomy plus orthotopic hepatic transplantation has been performed for cancers involving the liver. Nevertheless, only a small percentage of patients who have cancer in the liver are suitable candidates for any of these types of resection. Chemotherapy has been disappointing as primary treatment and radiotherapy cannot be administered in a high enough dose to destroy tumor in the liver without causing significant hepatic damage. Thus, there is a great need for alternative methods of treatment for cancer within the liver.

Cryosurgery has been used for many years to treat various types of tumors in different sites. The first use of cryotherapy was in the mid-19th century when ice water was used as treatment for breast and cervical cancer [1]. Clearly, this might have temporarily relieved pain but it had no long-term effects on the tumor itself. It was not until the 20th century, when liquid nitrogen became available, that temperatures cold enough to kill tumor cells could be achieved. The problem with using liquid nitrogen without good monitoring, however, was that the extent of the freeze could not be controlled well and assessment of the death of tumor cells could not be obtained when the freeze was ongoing. Furthermore, the technology was primitive and nitrogen emboli were reported [2].

Over the last few years the ability to perform cryotherapy has been greatly enhanced by the development of new technology that has allowed liquid nitrogen to flow within probes that can be placed directly into the tumor in the liver. This obviates the potential problem of gas embolization, and also allows determination of the location of the tip of the probe in relation to the tumor via either direct palpation for surface lesions or by the use of ultrasound for lesions that are deeper in the liver. Placement of the probe can be carefully controlled, and the extent of the freeze can be monitored either by ultrasound monitoring [3] or by using temperature transducers. All of these factors have permitted better freezing of tumors within the liver as well as improved monitoring of the freezing process.

At the same time technology was improving, understanding of the experimental basis of cryosurgery was also undergoing advances. It was found that the temperature needed to kill tumor cells was −40°C to −60°C, and that optimal tumor destruction by freezing was obtained with a freeze, thaw, and refreeze cycle [4]. Much as is the case with resection, to adequately destroy tumor cells requires the freezing of a rim of normal tissue adjacent to the tumor (a ‘‘margin’’). This minimizes the chance of local recurrence and can be accomplished using appropriate monitoring techniques.

What is the current role of cryosurgery in the management of tumors involving the liver? At this time it appears that cryosurgery is useful for patients whose tumors are confined to the liver but are unresectable for various reasons. These reasons include bilateral nature of the tumor, anatomic location of the tumor (such as at the bifurcation of the portal vein or in other areas that preclude resection), or presence of significant concomitant medical conditions. Patients with severe cirrhosis who are unable to undergo a major hepatic resection should be considered for cryosurgery of a hepatic malignancy.

The results of cryosurgery are remarkably similar to the results of resection for both primary and metastatic liver cancer. This is all the more remarkable because

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these patients are considered unresectable. Large series of patients with hepatoma have been reported to have about a 20% 5-year survival following cryotherapy [5], even higher when the tumor is smaller than 5 cm. Patients with metastatic colorectal cancer treated by cryotherapy have been reported to have about a 20% survival [6], and similarly treated patients with metastases from neuroendocrine carcinomas also have a good survival [7], although this is more difficult to interpret because these tumors have a better prognosis anyway.

The risks of hepatic cryotheraphy have been understated in the literature. Multiple complications have been seen [8], although most of them are quite infrequent. Common complications include myoglobinemia and myoglobinuria, seen in the vast majority of patients, and if this is not vigorously treated with diuretics and alkalinization of the urine, precipitation into the tubules can occur with renal dysfunction or even shutdown. Many patients will develop a pleural effusion; normally only a small percentage will require thoracentesis or chest tube placement. Other complications are less common, but include bleeding, infection, thrombocytopenia, and coagulopathy. Patients with impaired liver function to begin with have a higher chance of going into hepatic failure, but most of the time this problem can be treated with fresh frozen plasma and medical support for several days while the liver recovers. Some patients, however, will never be able to recover and will die. In our experience, this has been the case mainly in patients with large tumors and marked hepatic dysfunction preoperatively.

At the current time, hepatic cryotherapy should be used for patients who have liver neoplasms that are unresectable for reasons of bilaterality, location in the liver, or concomitant medical diseases. It should, generally, not be used when extrahepatic tumor is also present. Resection remains the treatment of choice for primary liver cancer and limited hepatic metastases from tumors such as colorectal cancer and neuroendocrine cancer, but some investigators feel that cryosurgery is as effective as resection. Nevertheless, the majority of patients who undergo cryosurgery will fail. This is usually not at the site of the cryosurgery, but at other sites in the liver, or even outside the liver. Thus, the addition of systemic therapy may be indicated. Several investigators are using chemotherapy to try to reduce disease recurrence, but prospective randomized trials have not yet shown this to be beneficial.

Other directions for cryosurgery research include trying to determine the cause of the myoglobinemia and myoglobinuria that follow cryosurgery. The liver contains very little muscle, and the high levels of myoglobin seen following cryosurgery cannot be coming from the liver. This could be related to cytokine release with subsequent myonecrosis [9], but the mechanism of this complication remains to be determined. Blocking such cytokines might minimize postoperative morbidity. At the current time, cryosurgery is usually performed through a large laparotomy incision. Investigations into performing cryosurgery laparoscopically are under way. However, the cryoprobe can be difficult to place, even with the liver being held in one's hands, and the laparoscopic ultrasound transducer does not give the same delineation of the liver and its lesions as the hand-held transducer will provide. The technology continues to improve, and cryosurgery should now be considered an important part of the liver surgeon's armamentarium; its use will probably increase in the future.

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